Developmental Biology 331 (2009) 467–469

Contents lists available at ScienceDirect

Developmental Biology

journal homepage: www.elsevier.com/developmentalbiology

Abstracts

Cell proliferation

Program/Abstract # 275

The checkpoint adaptor protein *Xenopus* Claspin is phosphorylated dependently on nucleocytoplasmic ratio

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The *Xenopus* midblastula transition (MBT) begins after the twelfth cleavage. The MBT marks cell cycle lengthening and loss of synchrony, and establishment of checkpoints. In somatic cells, the checkpoint kinase Chk1 is activated in response to unreplicated DNA. At the MBT, Chk1 is transiently activated. This activation is required for cell cycle remodeling at the MBT. When the DNA replication checkpoint is activated, Claspin recruits Chk1 for phosphorylation by the ATR kinase. However, Claspin's function during early embryogenesis remains unknown. Toward solving its function, we investigated Claspin expression and modification during embryogenesis. Claspin protein level is constant until the MBT, and then becomes phosphorylated at approximately the MBT. Although Claspin phosphorylation depends upon ATR when the DNA replication checkpoint is activated, its phosphorylation in the embryo is insensitive to caffeine, an ATR inhibitor. This phosphorylation depends on a critical nucleocytoplasmic ratio in cell-free egg extracts. To examine Claspin function during embryogenesis, we made mRNA encoding an inactive kinase domain of Chk1, which should bind to endogenous Claspin and inhibit binding of endogenous Chk1 to Claspin by a "dominant-negative" effect. Expression of the Chk1 fragment led to death at the time when control embryos underwent neurulation. Thus, we propose that the Claspin phosphorylation is an additional hallmark of MBT and suggest that Claspin is required for early embryonic development.

doi:10.1016/j.ydbio.2009.05.301

Program/Abstract # 276

Gdf11 affects the temporal progression of neurogenesis in the developing spinal cord

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During neurogenesis, various types of neurons and glia originate from the progenitor cells following a precise spatial and temporal order. The mechanisms that control the sequential generation of different neuronal and glial cell types from the same progenitor population are not well understood. Gdf11 is a member of the TGF-b family of proteins and is expressed transiently in newly born neurons located in the developing spinal cord. By examining the phenotypes of *Gdf11*$^{-/-}$ mouse embryos, we found that without Gdf11, a delay in the temporal progression of neuronal differentiation is present soon after the onset of neuronal differentiation. Higher numbers of progenitor cells, along with a delay in the onset of gliogenesis are also observed in *Gdf11*$^{-/-}$ spinal cord but only after the peak of *Gdf11* expression, indicating that Gdf11 can cause permanent changes in progenitor properties. Differences in proliferation rate and differentiation potential are observed between neurospheres derived from *Gdf11*$^{-/-}$ and wild-type littermates, and such differences can also be induced in wild-type neurospheres with the addition of Gdf11. We further provide evidence that Gdf11's effects on progenitor cells, at least in part, are mediated by its ability to up-regulate p57^{kip2} and down-regulate Pax6 expression. These results support a model in which Gdf11 secreted by newly born neurons in the developing spinal cord acts as a feed-back signal on the progenitor cells to promote cell cycle exit, in addition to changing their proliferation ability and differentiation potential and thus, influencing the temporal progression of neurogenesis.

doi:10.1016/j.ydbio.2009.05.302

Program/Abstract # 277

Development of the ventral hypothalamus and infundibulum

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The hypothalamo–pituitary system governs body homeostasis. The neuronal hypothalamus and endocrine pituitary are linked via the infundibulum. Compromised function of the hypothalamo–pituitary neuraxis gives rise to a huge variety of dysfunctions and disease states; however, while much is understood of the development of the anterior pituitary, little is known regarding the developmental programme of the infundibulum. Here I show that in the embryonic chick, the infundibulum is derived from two adjacent populations of hypothalamic floor plate cells. A population of midline hypothalamic floor plate cells expresses Fgf10, stops proliferating and forms the ventral/posterior infundibulum. A second population of Fgf3+ Sox3+ cells is located adjacent to the FGF10+ domain. These cells are proliferative and contribute to the dorsal/